DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

December 4, 2001

By Certified Mail—Return Receipt Requested CBER-02-003

Warning Letter

Walter D. Holder, M.D., Director
General Surgery Research
Carolinas Medical Center
1000 Blythe Boulevard
Charlotte, North Carolina 28203

Dear Dr. Holder:

During the period from August 27 to September 6, 2001, Eileen J. Bannerman and Tracy R. Ball, investigators from the Food and Drug Administration (FDA), inspected your conduct of clinical studies under IND —— The inspection was conducted under the FDA's Bioresearch Monitoring Program that includes inspections designed to review the conduct of research involving investigational products.

At the end of the inspection, a Form FDA 483 (enclosed) was issued to you. We determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR), Parts 50 and 312. The applicable provisions of the CFR are cited for each violation.

1. You failed to ensure that the investigation was conducted according to the general investigational plan and protocol contained in the IND. [21 CFR § 312.50].

a. You failed to follow IND —— HIGH RISK FOR RECURRENCE MELANOMA PATIENTS WITH —— —— MELANOMA VACCINE —— ' when you administered melanoma vaccine ——

i. You administered melanoma vaccine —— to six subjects (—— 95-06, —— 95-12, —— 95-16, —— 97-01, —— 98-09, and —— 99-06) whom you enrolled on Protocol —— You did not amend the IND, as required by 21 CFR § 312.30.

b. You enrolled 94 subjects into Protocol ———, "Melanoma ——— CMVAC (Carolinas Melanoma Vaccine) Melanoma Vaccine ——— " without submission of this new protocol to the FDA for review, as required by 21 CFR § 312.30(a).

We acknowledge that you asked the FDA whether you were required to obtain a new IND for melanoma vaccine ——— ——— in correspondence to Protocol ——— However, by the time of your request, you had already enrolled 84 subjects into Protocol ———

c. You failed to perform quality control testing for the investigational vaccine as required by protocol. One lot of investigational vaccine was contaminated with *Staphylococcus epidermidis*, but was administered to 38 subjects.

d. You failed to measure serum antibody titers every — months, as specified by protocol.

e. You failed to ensure that the investigational vaccine was manufactured in accordance with specifications in Protocol ———

Protocol ——— states, "For each of the — cell types, — samples were prepared..." However, the inspection revealed that approximately — samples were prepared for each cell line.

The protocol states, "All Culture Tests were done ——— while cells were in culture and on batch quantities to be used for ———." The inspection revealed that each cell line has been tested only twice, in ———

iii According to the protocol, the following tests were to be performed on batch quantities of the product: "Routine, —— and fungal cultures off ——— ' The inspection revealed that analyses for bacteria and fungi were done for only ——— lots of the investigational vaccine.

f You failed to meet the requirement of Protocol ——— to have a study monitor review the Case Report Forms (CRFs) every — months. The inspection revealed that this review was not done.

2. **You failed to ensure that the investigation was conducted according to the investigational plan (protocol). [21 CFR § 312.60].**

You failed to administer — to subject —-98-21 according to the protocol. Although you gave an initial dose of — to this subject, you failed to administer any subsequent doses of —

3. **You failed to maintain adequate case histories. [21 CFR § 312.62(b)].**

a. You failed to document the occurrence of adverse events on the CRFs. Examples are given below:

According to patient progress notes, subject —'-97-09 experienced "fever, chills, increasing shoulder pain and malaise of the injection site." In addition, he required surgical incision and drainage of "cloudy material" out of the injection site.

ii. Patient progress notes state that subject — 00-36 was "sick for 2 weeks and had diarrhea and fatigue" requiring bed rest.

Protocol —— states that the —— was changed from —— in order to decrease the number of adverse events. In order to compare the —— you must document all adverse events.

b. The inspection revealed numerous examples where new entries were written over previous ones on the CRFs. In addition, white correction fluid was used to obscure entries on CRFs.

c. You failed to maintain all source documents to verify the information entered on the CRFs.

There are no source documents to verify entries on CRFs for subjects —-95-05 (Skin Test Form #2) and — -99-04 (—— Form).

ii. There are discrepancies between source documents and CRF entries for subject — 00-13 with regard to which arm was used for the "Application Site."

iii. For subject — 99-01, the expiration date of the ——— lot was not recorded in the space provided on the CRF. Instead, the notation "Discarded" was written.

d. During the inspection, you were unable to provide a complete version of Protocol ——— that you had previously submitted to the FDA.

4. **You failed to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR § 312.60].**

You failed to protect the rights of subject ——95-12 when the subject signed an informed consent document for the wrong investigational product. The subject signed the consent form entitled "Consent for Melanoma ——— ——— yet you administered the investigational product melanoma vaccine ——— There is a handwritten note, without a date, inserted at the top of the first page of the form stating, "Pt received ——— Pt aware." There was no Institutional Review Board review or approval of this consent form modification. See item 1a above.

5. **You failed to maintain adequate records showing the disposition of the investigational drug. [21 CFR §§ 312.57(a) and 312.62 (a)].**

a. You failed to maintain product accountability records in the clinic for the quantity of the test article and the date of receipt.

b. You failed to document the destruction of the contaminated vials of Protocol ——— batch number —

6. **You failed to provide a complete list of the subinvestigators who assisted you in the conduct of the investigations. [21 CFR § 312.53(c)(1)(viii)].**

The inspection revealed that you did not have a Form FDA 1572 to identify that Dr. Gerald Sonnenfeld assisted you in Protocol ——— In addition, the only Form FDA 1572 listing Dr. Didier Dreau as a subinvestigator was dated 8/21/01, after —— years of participation as a subinvestigator in Protocols ———

This letter is not intended to be an all-inclusive list of deficiencies. It is your responsibility to ensure adherence to each requirement of the law and applicable regulations. You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in enforcement action without further notice. These actions could include termination of Investigational New Drug Applications and/or injunction.

You should notify this office in writing, within fifteen (15) business days after receipt of this letter, of the specific actions you have taken to correct the noted violations. If corrective action cannot be completed within fifteen (15) business days, state the reason for the delay and the time within which the corrections will be completed. Your response should include any documentation necessary to show that correction has been achieved.

Failure to achieve correction may result in enforcement action without further notice. The actions could include initiation of investigator disqualification proceedings which may render a clinical investigator ineligible to receive investigational new drugs.

Please send your written response to:

Mary Andrich, M.D. (HFM-664)
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville, Maryland, 20852
Telephone: (301) 827-6221

We request that you send a copy of your response to the Food and Drug Administration's Atlanta District Office at the address below.

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosure:

Form FDA 483, Inspectional Observations, dated September 6, 2001

cc:

Wallace C. Nunley, M.D., Chairman
Institutional Review Board
Carolinas Medical Center
1000 Blythe Boulevard
Charlotte, North Carolina 28203

Ballard H. Graham, Director
Food and Drug Administration
60 Eight Street, N.E.
Atlanta, Georgia 30309